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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,023	06/28/2001	Vladmir R. Muzukantov	PENN-0749	7329

26259 7590 02/06/2004

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,023	MUZUKANTOV ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Maher Haddad, Art Unit 1644, Technology Center 1600.

2. Applicant's amendment, filed 7/09/03, is acknowledged.

3. Claims 5-6 are pending and under examination in the instant application.

4. In view of the amendment filed on 7/09/03, only the following rejections are remained.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 5-6 stand rejected under 35 U.S.C. 1 12, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was tiled, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 1/16/03.

Applicant is in possession of a method for dissolution of fibrin clots by administering a non-internalizable antibody to ICAM-1 and a fibrinolytic or anti-coagulant.

Applicant is not in possession of a method for augmenting local "anti-thrombotic potential" of endothelium and dissolving of intravascular blood clots in the pulmonary vasculature of an animal comprising intravenously administering to the animal a fibrinolytic or anticoagulant agent conjugated with an antibody which binds to any "antigen" on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cells in claim 5.

Applicant has disclosed only anti-ICAM-1 monoclonal antibody, mAb 1A29 as non-internalizable antibody; therefore, the skilled artisan cannot envision all the contemplated non-intrnalization antibody which binds to any antigen on the luminal surface of the vascular endothelium possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method.

Applicant's arguments, filed 7/09/03, have been fully considered, but have not been found convincing.

Applicant submits that the specification on page 9, lines 9-20 defines non-internalizable antibodies as antibodies which bind to an antigen on the luminal surface of the pulmonary vasculature and which are determined not to be internalized by cultured human endothelial cells

as described in the application and/or shown be temperature independent in pulmonary uptake experiments isolated lung perfusions as also described. Applicant concludes that both structure of this genus of molecules, an antibody, and a functional characteristic of this genus of molecules , binding to an antigen on the luminal surface of the pulmonary vasculature, which is not internalized, are taught by the written description of the application. Therefore, the written description requirement for the claimed genus of non-internalizable antibodies satisfied by this disclosure.

However, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, non-internalizable antibody that binds to an antigen on the luminal surface of the vascular endothelium and it's targeting delivery function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of antibodies, wherein the antibodies bind to an antigen on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cells such features essential to the instant invention. The specification, on page 6, lines 6-7, discloses that lack of internalization is an obligatory for therapeutic action of fibrinolytics and anticoagulants. No such antibodies were made or shown to have such characteristic. Only the mAb 1A29 is disclosed. Such does not constitute an adequate written description for the claimed non-internalizable antibodies that binds to an antigen on the Luminal surface of the vascular endothelium.

7. Claims 5-6 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for dissolution of fibrin clots by administering a non-internalizable antibody to ICAM-1 and a fibrinolytic or anti-coagulant does not reasonably provide **enablement** for a method for augmenting local "anti-thrombotic potential" of endothelium and dissolving of intravascular blood clots in the pulmonary vasculature of an animal comprising intravenously administering to the animal a fibrinolytic or anticoagulant agent conjugated with an antibody which binds to any "antigen" on the luminal surface of the vascular endothelium

without subsequent internalization into endothelial cells in claim 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 1/16/03.

Applicant's arguments, filed 7/09/03, have been fully considered, but have not been found convincing.

Applicant argues regarding using a non-internalizable antibody other than anti-ICAM-1, that the specification and one skill in the art can identify claims as to routinely additional non-internalizable antibodies useful in the claimed method of the present invention. Applicant directs the Examiner's attention to page 9, lines 9-20 of the specification wherein taught that a non-internalizable antibody useful the present invention can be identified by determining its ability to bind to an antigen on the luminal surface of the pulmonary vasculature, ability not to be internalized by cultured human endothelial cells (methods of which are set in Example 2 or the specification) and/or temperature independence in pulmonary uptake experiments isolated lung perfusions (methods of which are set forth Example 3 the specification). Applicant contends that such methods can be performed routinely by those skill in the art and do not constitute undue experimentation.

Regarding applicant's argument that that the specification provides a working example and substantial guidance on how to identify non-internalizable antibodies that binds to the surface of endothelial cells that have the recited properties, the examiner notes that in order to satisfy the U.S.C 112, 1st paragraph, the specification has to teach how to make and/or use the invention, not how to screen to identify the invention. Until the time when such non-internalizable antibodies are found, then one skill in the art can make them. Further, the specification on page 3, provides examples of non-internalizable antibodies such as anti thrombomodulin, E-selectin and PECAM, 3pev antigens.

Applicant directs the examiner's attention to Murciano et al. Crit. Care, October 1, 2001 163:1295-1302) to demonstrate the use of different antibody, which binds not ICAM-I, but to a distinct antigen (GP85) on the luminal surface the vascular endothelium without subsequent internalization into endothelial cells in vascular immunotargeting. Further, Applicant points out to Murciano (Blood, 2003 MS 2002-09-2853) to confirm that anti-ICAM-l vasculature after injection in mice and did not undergo internalization. Applicant concluded that the ability of one of skill in the art to make and use other non-internalizatble antibodies beside anti-ICAM-1 in the invention commensurate in the scope with the claims.

The Examiner acknowledges that these references do provide some support non-internalizable anti-GP85 antibody, mAb 30B3. However, such antibody was not disclosed in the specification as originally failed. The specification should be enabled at the time the invention was made. Regarding Murciano (Blood, 2003 MS 2002-09-2853), is inconsistent with the specification that use of non-internalizable anti-ICAM-1 antibody is enabled for the method of dissolution of fibrin clots.

Regarding methods of prevention, Applicant argues that the ability augment the thrombotic potential blood clots has also been confirmed endothelium and dissolve intravascular animals. Results from these experiments were recently published online in Blood 2002-09-2853 (discussed above). Applicant points to Figure 9 of this paper wherein demonstrated that enzymatically active anti-ICAM/tPA conjugate accumulated fibrinolysis of fibrin emboli lodged in rat lungs.

However, "anti-thrombotic potential" still reads on "prevention of intravascular coagulation" the cited reference provides enablement only for the treatment method but not prevention as indicated by applicant argument above that enzymatically active anti-ICAM/tPA conjugate accumulated fibrinolysis of fibrin emboli *lodged* in rat lungs.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bowes et (Neurology 1995) of Imaizumi (Transpl. Proc. 1994), Mulligan et al (Amer. Pathol. 1993), and Panes (Amer. Physiol. 1995), and further in view of Runge et al and Torchilin et al, and Muzykantov et al (BBA 1986), and Muzykantov et al (Amer J Physiol, 1996).

Bowes *et al* teach that administration of an anti-lCAM-1 mAb and the drug tPA to rabbits prevents leukocyte adhesion and increases post ischemic duration at which thrombolytic therapy remains effective in cerebral ischemia and reperfusion (especially Abstract). Bowes *et al* also teach that administration of tPA alone improves neurologic outcome in models of ischemia, but that obstacles exist to therapy, and further that reperfusion may also result in additional neurologic damage as ischemic tissue is reoxygenated.

The claimed invention differs from the Bowes *et al* teachings only by the recitation of administering to an animal a fibrinolytic or anticoagulant agent conjugated with an antibody which binds to an antigen on the luminal surface of vascular endothelium without subsequent interanalization into endothelial cells.

Imaizumi teaches a method of administration of mouse anti-rat mAb 1A29 (anti-ICAM-1) inhibits ICAM-I on pulmonary vascular endothelial cells and impairs damage due to reperfusion injury. Imaizumi teaches that impairment of reperfusion injury is closely associated with vascular endothelial cell damage by neutrophils. lmaizumi further teaches that in flowing blood, neutrophils do not adhere to vascular endothelial cells in the normal state; adhesion of neutrophils to vascular endothelial cells is necessary to induce vascular endothelial cell damage after ischemia and reperfusion, and an increase in the expression of adhesion molecule (especially page 1853, column 1). Imaizumi teaches an increase in the expression of adhesion molecules in vascular endothelial cells activated by reperfusion and a resultant increase in the binding to neutrophils.

Mulligan *et al* teach anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, i.e., binds to the luminal surface of the endothelium and is not internalized, challenged with pro-inflammatory agents, and that blocking of ICAM-1 is tissue protective in a manner in which neutrophil recruitment is attenuated. Mulligan et al further teaches that the radiolabeled anti-ICAM-1 (1A29) antibodies were intravenously injected (page 1741, under in vivo ICAM-1 quanitifcation).

Panes *et al* teach that ICAM-I is constitutively expressed on vascular endothelium of the rat and there are significant regional differences in magnitude of expression.

Runge *et al* teach the thrombolytic drug tPA can be efficiently directed to the site of a thrombus by conjugation, i.e., chemical modification, to an anti-fibrin monoclonal antibody, resulting in both more potent and more selective thrombolysis (especially Abstract).

Torchilin *et al* teach that targeted accumulation of thrombolytic enzymes in the region of thrombus location can be achieved by their coimmobilization with specific antibodies (especially Abstract). Torchilin et al further teach drawbacks in administration of tPA alone include necessity of prolonged and continuous administration due to rapid physiologic inactivation far from the site of thrombolysis (especially page 322) may be resolved by the use of antibody-immobilized tPA.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the tPA to a mAB (such as 1A29) as taught by Torchilin et al, or for Runge et al and Muzykantov *et al* for fibyrolytic agents or for other molecules recognizing mAb specific for target molecules on vascular endothelium using chemical modification as taught by Muzykantov et al or Runge et al. and further, substitute the resultant conjugate for the anti-ICAM-1 mAB in the composition of Bowes et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because ICAM-1 is constitutively expressed on vascular endothelium as taught by Panes *et al.* and to prevent the deleterious side effects of administering tPA alone as taught by Torchilin et al or to more effectively target the tPA to regions of the vascular bed having an increased probability of clot formation as taught by Muzykantov et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 7/09/03, have been fully considered, but have not been found convincing.

Applicants respectfully traverse these rejections base on the ground the combination of cited references teach or suggest all the limitation of the amended claims. Specifically, Applicant argues that none of the cited references teach or suggest conjugation of the therapeutic agent. Applicant further contends that each of the cited prior art references, the effects of a fibrinolytic agent were examined alone and when co-administered with an antibody. Applicant asserts that no wehere the effects of conjugating a thrombolytic agent with an antibody targeted to a poorly internalized antigen of the endothelium taught or suggested.

Contrary to applicant assertions the combined teachings of the references arrived to the claimed method. Given that the conjugation of a drug (such as tPA) can be efficiently directed to the site of a thrombus by conjugation, i.e., chemical modification, an anti-fibrin mAb which result in both more potent and more selective thrombolysis taught by Runge et al. and given that anti-ICAM-1 mAb 1 A29 accumulates in the pulmonary vasculature, i.e., binds to the luminal surface of the endothelium and is not internalized as taught by Mulligan et al, and given that the administration of 1A29 mAb inhibits ICAM-1 on pulmonary vascular endothelial cells and impairs damage due to reperfusion injury as taught by Imaizumi et al, wherein ICAM-I is constitutively expressed as taught by the Panes *et al* reference and given the method of Bowes et al. One of ordinary skill in the art at the time the invention was made would have been motivated to combined the references teachings to arrive the claimed invention as discussed supra.

Applicant argues each reference individually that nowhere does each reference teach or suggest targeting the luminal surface of pulmonary vascular endothelium with a drug conjugated to a non-internalizable antibody or targeting the luminal surface of pulmonary vascular endothelium wit a drug conjugated to a non-internalizable antibody.

However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is

what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (571) 272-0845. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (571) 272-0841. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9307.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
February 2, 2004

Christina Chan

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